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Longitudinal evaluation of cognitive disorder in Huntington's disease

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Abstract

The study investigated longitudinal change in cognitive function in 87 patients with Huntington's disease (HD), using a range of neuropsychological tests, which tap mental manipulative abilities, memory, and frontal executive skills. Over a 1-year period the largest changes were noted in letter fluency, object recall, and Stroop Test performance, whereas no changes were noted over more than 3 years on the modified Wisconsin Card Sorting Test. Contrary to expectation, greater change was evident over 1 year for tasks with low compared to high cognitive demands. The differential sensitivity of tasks was attributed in part to inherent characteristics of the tests themselves: their capacity to detect minor gradations of change and their vulnerability to practice effects. However, the greater change for relatively automatic, speed-based tasks with low cognitive demands was interpreted as reflecting the evolution of HD, with a greater magnitude of change occurring in basal ganglia than cortical function. One purpose of the study was to identify tasks sensitive to the progression of HD and hence most suitable for the evaluation of therapies. Despite reaching statistical significance by virtue of the large group size, numerical differences in test scores over 1 year were very small, suggesting that the use of such tests to evaluate change in individuals or small groups of subjects would be problematic. The data highlight the slow progression of HD, the limitations of standard cognitive tests in detecting change over short periods, and the need for therapeutic studies that encompass a relatively prolonged time frame. (*JINS*, 2001, *7*, 33–44.)

Keywords: Huntington's disease, Cognition, Progression, Basal ganglia

INTRODUCTION

Huntington's disease (HD) is an autosomal dominant degenerative disorder which gives rise to motor abnormalities and alterations in mood and cognition. Although the choreiform movements are the hallmark of HD, it is the mental changes that often represent the most disabling aspect of the condition and place the greatest burden on HD families.

Isolation of the gene responsible for HD (The Huntington's Disease Collaborative Research Group, 1993) has raised prospects for treatment. In recent years, efforts have been made to develop surgical treatments involving transplantation of striatal neurones (Dunnett et al., 1988; Hantraye et al., 1992; Isacson et al., 1986; Sirinathsinghji et al., 1988) as well as new pharmacological therapies (Feigin et al., 1996; Kierburtz et al., 1996). If therapies are to be successful, they will need to have a beneficial effect not only on the movement disorder but also on cognition. It will be essential for the evaluation of therapeutic efficacy to have a better understanding of the natural history of the cognitive disorder in HD patients and to identify test measures which are most sensitive to and best reflect changes over time.

The nature of the cognitive disorder in Huntington's disease has been well documented (Brandt & Butters, 1986; Brandt et al., 1988; Jacobs & Huber, 1992; Lange et al., 1995; McHugh & Folstein, 1975; Paulsen et al., 1995; Sprengelmeyer et al., 1995). Patients exhibit impairments particularly in the regulation of mental function, manifest by deficient performance on frontal executive tasks and in memory retrieval. However, there have been relatively few longitudinal studies of cognitive change. There remains a need to clarify how different aspects of cognition change over the course of the disease, and whether test measures which are known to be sensitive to the presence of HD are also

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useful in measuring change over time. It is particularly relevant for evaluation of therapeutic efficacy in a disorder which is relatively slow in its progression to ascertain whether reliable changes can be detected over a period as short as 1 year. The purpose of the present study was to address these issues.

METHODS

Patients

The study involved 87 patients with clinically diagnosed and genetically confirmed HD, who attend a regional HD clinic and participate in a prospective longitudinal study of cognitive, motor, and behavioral change in HD (Tables 1 and 2). All patients had been followed up for a minimum period of 1 year and had undergone neuropsychological assessments at least two occasions 1 year apart. The study cohort constituted consecutive referrals, with the exception that individuals over 70 years of age were excluded to avoid potentially confounding effects of independent age-related changes in cognitive function. All subjects had attended mainstream schools and had at least 10 years formal education. Patients encompassed a range of illness severity as measured by the Functional Capacity Scale (Shoulson & Fahn, 1979; Shoulson, 1981), although most patients fell into the mild-to-moderate range, the mean score of 9 corresponding to stage II illness.

A subgroup of 31 patients had been assessed on at least four occasions, each assessment being at least 1 year apart, providing longer term follow up data over a minimum of 3 years for this smaller group.

Control Subjects

A group of 55 individuals at risk from HD (Table 1), who had undergone predictive testing and were found not to be carriers of the HD gene, served as controls for a cross-sectional analysis of patients' baseline (first test) performance. The rationale for choice of reference group was to match subjects as closely as possible for social background: people growing up in HD families may experience disruptions to their education and family life, with potentially adverse effects on cognitive performance. Control subjects did not differ significantly from the affected HD patients with respect to age ($t = 1.4$ $p > .1$). However, they did differ with respect to sex distribution ($\chi^2 = 5.6$, $p = .018$). The disproportionate representation of female subjects in the control group reflects the greater number of women than men who choose to take the predictive test for HD.

Table 1. Demographic information

	HD patients	Unaffected controls
No.	87	55
Sex	51 males	21 males
	36 females	34 females
Age		
mean ± *SD* (range)	45 ± 12 (18–69)	42 ± 9 (31–67)

Table 2. HD background information[a]

	Mean ± *SD*	Range
Age at onset of illness	40 ± 12	13–64
Duration of illness (years)	5 ± 3	1–17
CAG repeat length	46 ± 5	36–68
Total functional capacity (TFC)	8 ± 3	2–13
QNE motor impairment scale (median = 6.5)	7 ± 4	0–17
NART error score	30 ± 12	6–44

[a]QNE: Quantitated Neurological Examination; NART: National Adult Reading Test (Nelson & O'Connell, 1978; Nelson, 1982).

Neurological Examination

Patients' neurological status was assessed early in the study, using the Quantitated Neurological Examination QNE (Folstein et al., 1983), from which measures of chorea (Chorea Scale) and non-choreic motor impairment [Motor Impairment Scale (MIS)] can be derived. The chorea scale (range 0–25) elicits a score of 0 in healthy control subjects, whereas the MIS (range 0–28), which measures voluntary movement, such as motor speed, fine motor control and gait, yields a mean normal score of 0.4. For recently recruited subjects, neurological findings were recorded using the motor scale of the Unified Huntington's Disease Rating Scale (UHDRS) (Huntington's Disease Study Group, 1996), with the addition of items that would allow for the continued calculation of the MIS measurement.

Neuropsychological Assessment

The cognitive assessment emphasized frontal executive and mental manipulative skills, memory, and psychomotor speed. It comprised published tests that are widely recognized to be sensitive to the presence of HD (Bamford et al., 1989; Brouwers et al., 1984; Butters et al., 1978; Bylsma et al., 1992; Josiassen et al., 1983; Starkstein et al., 1988), together with some nonstandardized tasks, found in cross-sectional investigations to be sensitive to the presence of HD. The tests were as follows:

1. Recitation of the months of the year (a) forwards and (b) in reverse order. Performance was measured in terms of time to complete the series. The number of errors was also recorded, but in view of their rarity were not subjected to statistical analysis.
2. Digit span forwards and backwards. The standard procedure of administration was adopted, as for the Wechsler Adult Intelligence Scale (revised) Digit Span Subtest (Wechsler, 1981).

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3. Standardized Road Map Test of Directional Sense (Money, 1976). This test requires the subject to track a diagrammatic road map and to make left–right judgments about turns on the map. Judgments necessitate mental spatial rotations of 0, 90, or 180 deg. Performance was measured in terms of accuracy (percent correct), and time to complete the task. In a separate condition, involving comparable motor but reduced cognitive demands, the subject was asked to trace the road map, without the requirement to make left–right judgments. Tracing time was recorded.

4. Object recall. The subject was shown a random display of 20 real objects for 30 s, following instructions to look carefully at each object since memory would subsequently be tested. Free recall was tested immediately following presentation and again after a 30-min delay filled with other tasks. No feedback was given. Performance was measured in terms of the number of items correctly recalled. Intrusion errors and perseverative responses were also recorded, but in view of their rarity were not subjected to statistical analysis.

5. Story recall. The subject was asked to read aloud a fable-like short story (Talland, 1965; Talland & Ekdahl, 1959) following instructions to concentrate on its content since memory would subsequently be tested. Free recall of the story, divided into 14 basic units, was tested immediately following the reading, and again after a 30-min delay filled with other tasks. Performance was scored in terms of the number of content ideas correctly recalled.

6. Category fluency. The subject generated as many names of animals as possible in 1 min. The score represents the number of correct responses.

7. Letter fluency. The subject generated in 1 min words beginning with F. Administration and scoring followed the standard procedure (Benton & Hamsher, 1989; Spreen & Strauss, 1991). Proper nouns and derivations of the same word stem were not admissible.

8. Wisconsin Card Sorting Test (Nelson, 1976). This version of the test, in which the subject sorts cards according to shape, color, or number, differs from the original (Berg, 1948) in that (a) there are 48 cards in the response set; (b) no response card shares more than one common feature with a key stimulus card; (c) rule shifting, of which the subject is forewarned, takes place after six successive correct responses; and (d) perseverative errors are defined as incorrect responses which follow the rule of the immediately preceding response (not necessarily the previous correct category). Performance was measured in terms of categories achieved, total errors, and percentage of perseverative errors. In addition, the test was timed, yielding an overall completion time measure. Although the test is conventionally discontinued when six categories are achieved, in this study it ended only when all 48 cards had been placed, to allow for meaningful comparisons between completion time measures. The subject was then asked to deal the pack of cards into four piles. The time to deal cards yielded a measure of psychomotor speed in a task in which cognitive demands are minimized.

9. Picture Sequencing Test. This test, developed primarily for speech pathologists, is similar to the Picture Arrangement Subtest of the Wechsler Adult Intelligence Scale, but uses colored, visually clearer pictures (Learning Development Aids, 1975). It has been found to be highly sensitive to frontal lobe deficits in patients with degenerative brain disease (Snowden et al., 1996).

10. Stroop Test. The test followed the original procedure (Stroop, 1935), which includes four conditions:

    (i) reading color words printed in black ink (word 1 read).

    (ii) reading color words printed in colored ink (word 2 read).

    (iii) naming blocks of color (CB name).

    (iv) naming ink color of incongruous color words (CW name). This is the "interference" condition.

As in the original version, five colors were used. Practice items, consisting of a single row of ten items, familiarized the subject with the task. Test items were then presented on a sheet containing 100 items, arranged in ten rows. The time to read/name ink color of all items on the test sheet and the number of errors were recorded. Errors for the CW name interference condition only were subjected to statistical analysis, because of the small number arising for other conditions.

Analysis

Statistical analyses were carried out using the SPSS-PC software package. Nonparametric procedures (Siegel, 1956) were adopted because the data were not normally distributed, and ordinal scaling would allow inclusion of data from the most severely affected patients with floor-level scores. The Wilcoxon Matched-Pairs Signed-Ranks Test was used to compare test performance over time. A One-Tailed Test was adopted because the analysis was concerned only to identify change in a negative direction: deterioration in performance from one test to the next. Multiple regression analysis was used to evaluate the influence of a range of variables on the extent of cognitive change. A standard rather than stepwise procedure was adopted, as recommended by Tabachnick and Fidell (1996), since the primary purpose was to address the question of multiple correlation rather than model building. The Spearman rank correlation coefficient (r_s) was used for cross-sectional assessment of the relationship between cognitive test scores and measures of motor impairment.

A complete data set was not available for all subjects. Tests omitted resulted from logistical constraints imposed by the clinic setting and did not reflect failures of compliance on the patients' part. The Stroop Test was most often omitted since this was administered last in the testing session.

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RESULTS

Cross-Sectional Analysis of Cognitive Performance

Comparisons between performance on each of the cognitive tests and that of healthy control subjects are shown in Table 3. Statistically significant group differences were demonstrated on all tests, and the majority of test measures yielded differences greater than $p < .001$. The only exceptions were the accuracy measure on the Road Map Test, the percentage of perseverative responses on the Wisconsin Card Sorting Test, and the number of errors committed on the interference CW name condition of the Stroop Test. The data confirm the sensitivity of tests to the presence of HD.

Performance on many of the tests was measured in terms of time, and motor slowing is likely to contribute substantially to group differences. However, attempts were made to control for motor response time by calculating the difference between time to complete easy and difficult tasks with comparable motor demands (months backwards–forwards completion time; Road Map completion-tracing time; Wisconsin Card Sorting Test completion-dealing time; Stroop CW-CB name time). Significant differences in performance times between early HD patients and controls still remained. These findings indicate the presence of cognitive as well as motor slowing in HD. To determine whether slowing was disproportionate for more demanding tasks, the ratio of completion times for difficult and easy tasks was calculated (e.g., months backwards/months forwards completion time). HD patients took on average 3.6 times longer to produce the months of the year in reverse order than in a forward direction, whereas control subjects took 2.8 times as long. This difference in ratio reached statistical signifi-

Table 3. Baseline median test scores for HD patients and controls[a]

		HD baseline		Controls		Mann-Whitney *U*	
Test	Task condition	Median	Range	Median	Range	*z*	*p*
Months	forward completion time	9	4–25	5	4–12	7.2	.000***
	back completion time	30	8–>	12	7–32	6.6	.000***
	back-forward time	15	4–>	7	1–23	4.8	.000***
Digit span	forwards	5	3–9	7	4–10	6.2	.000***
	backwards	3	1–7	4	3–7	6.4	.000***
Road Map	% correct #	75	31–100	88	19–100	3.1	.001**
	completion time	150	40–>	66	39–252	6.9	.000***
	tracing time	37	11–140	17	10–36	5.7	.000***
	completion-tracing time	95	24–>	49	15–216	3.9	.000***
Object recall	immediate (max 20)	7	3–12	12	7–17	9.0	.000***
	delayed (max 20)	5	0–12	11	5–15	8.4	.000***
Story recall	immediate (max 14)	5	0–14	10	2–14	5.7	.000***
	delayed (max 14)	4	0–14	10	2–14	6.0	.000***
Word fluency	animals/1 min	11	3–25	21	9–35	7.5	.000***
	F words/1 min	6	0–19	14	4–28	7.2	.000***
Wisconsin Card Sorting Test	categories (max 8)	3	0–7	6	0–8	5.0	.000***
	total errors (max 48)	21	1–48	7	0–41	4.4	.000***
	% perseverations	27	0–100	20	0–77	2.0	.023*
	completion time	494	175–>	215	120–545	7.4	.000***
	dealing time	78	32–270	40	18–107	6.5	.000***
	completion-dealing time	342	135–>	165	98–438	4.6	.000***
Picture sequencing	errors (max 24)	4	0–22	1	0–7	5.5	.000***
	completion time	240	75–>	107	58–313	7.9	.000***
Stroop	word 1 read time	74	40–520	50	34–110	6.0	.000***
	word 2 read time	76	46–600	48	36–140	6.1	.000***
	CB name time	117	74–760	66	46–223	7.0	.000***
	CW name time	213	105–800	111	72–357	5.6	.000***
	CW name errors	4	0–64	1	0–20	3.2	.001**
	CW-CB name time	88	−15–415	50	20–150	3.0	.002**

[a]max: maximum score possible; # chance level performance = 50% correct. For completion times ">" implies that time exceeds cut-off for task (usually indicating failure to complete the task). Stroop: Word 1 = words in black ink, words 2 = words in color ink, CB = color blocks, CW = color words (interference condition). *p* values are shown to 3 decimal places; $p = .000$ implies that $p < .0005$.
***$p < .0005$; **$p < .01$; *$p < .05$.

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cance ($z = 1.9$, $p = .03$, one-tailed test). However, the Wisconsin Card Sorting completion/dealing time, the Road Map completion/tracing time, and the Stroop CW/CB name time showed no differences between HD patients and controls. Thus, although the HD patients were slower in absolute terms, reflecting a general psychomotor slowing, they did not show proportionately greater slowing for more cognitively demanding tasks.

Cognitive Change Over 1 Year

In the HD patients several tests yielded significant changes over 1 year (Table 4). The largest changes occurred in verbal fluency, in object recall, and in Stroop Test performance. Letter fluency yielded a bigger change than category fluency. In object recall, the significant effect was present for both immediate and delayed recall performance. On the Stroop Test, the greatest change occurred for the least cognitively demanding conditions and the least change for the most demanding CW name condition. Mildly significant changes were present also for the nondemanding speed-based tasks of months recitation, map tracing, and card dealing. In contrast, measures of cognitive decision time, calculated by subtracting speed of performance on low-demand from high-demand task (months backwards–forwards completion time, Road Map completion-tracing time, Wisconsin Card Sorting Test completion-dealing time, Stroop CW-CB naming time) revealed no change in the predicted direction. None of the three tests involving mental manipulation of information (months reversal, digit span reversal and Road Map Test of Directional Sense) revealed significant change over 1 year. Moreover, the modified Wis-

Table 4. Change in cognitive test performance over 1 year[a]

		Test 1		Test 2		Wilcoxon	
Test	Task condition	Median	Range	Median	Range	*z*	*p*
Months	forward completion time	9	4–25	9	3–30	2.2	.01*
	back completion time	30	8–>	31	8–>	1.4	n.s.
	back-forward time	15	4–>	14	2–>	0.7	n.s.
Digit span	forward	5	3–9	5	3–8	2.0	.02*
	backward	3	1–7	3	1–6	1.3	n.s.
Road Map	% correct #	75	31–100	78	41–100	1.7	(.05)
	completion time	150	40–>	142	37–>	0.0	n.s.
	tracing time	37	11–140	43	14–200	1.9	.03*
	completion-tracing time	95	24–>	85	23–>	1.8	(.04)
Object recall	immediate (max 20)	7	3–12	6	1–13	3.2	.001**
	delayed (max 20)	5	0–12	4	0–11	3.4	.001**
Story recall	immediate (max 14)	5	0–14	4	0–14	1.9	.03*
	delayed (max 14)	4	0–14	4	0–14	2.6	.005**
Word fluency	animals/1 min	11	3–25	10	2–23	3.3	.001**
	F words/1 min	6	0–19	5	0–15	4.3	.000***
Wisconsin Card Sorting Test	categories (max 8)	3	0–7	3	0–8	0.1	n.s.
	total errors (max 48)	21	1–48	18	1–48	0.7	n.s.
	% perseverations	27	0–100	30	0–100	0.7	n.s.
	completion time	494	175–>	454	150–>	0.1	n.s.
	dealing time	78	32–270	90	44–>	1.7	.05*
	completion-dealing time	342	135–>	302	92–1380	1.7	(.04)
Picture sequencing	errors (max 24)	4	0–22	4	0–22	2.8	.003**
	completion time	240	75–>	260	103–>	1.8	.04*
Stroop	word 1 read time	74	40–520	80	48–650	3.8	.000***
	word 2 read time	76	46–600	90	6–700	3.5	.000***
	CB name time	117	74–760	135	64–730	2.7	.003**
	CW name time	213	105–800	250	110–>	1.4	n.s.
	CW name errors	4	0–64	4	0–90	0.4	n.s.
	CW-CB name time	89	−58–415	100	−190–360	0.3	n.s.

[a]max: maximum score possible; # chance level performance = 50% correct. For completion times ">" implies that time exceeds cut-off for task, usually indicating failure to complete the task. Wilcoxon *z* scores are expressed as positive numerals for clarity. *p* values are shown in parenthesis if change in performance is not in the predicted direction of poorer performance on Test 2 than Test 1. n.s.: not significant ($p > .05$). *p* values are shown to 3 decimal places; $p = .000$ implies that $p < .0005$.
***$p < .0005$; **$p < .01$; *$p < .05$.

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consin Card Sorting Test showed no change, regardless of whether performance was measured in terms of categories achieved, total errors, perseverations, or time to complete the task.

Influence of Age, Gender, Premorbid Ability, and Markers of Disease Severity on Cognitive Change

The subject group encompassed a spectrum of ages and illness severity at the time of their initial assessment. To determine the degree to which the presence of detectable change over a 1-year period was influenced by a number of independent variables, including estimated premorbid ability and the stage of disease, standard multiple regression analyses were undertaken. The dependent variable was the absolute measure of change on each cognitive test (time 2 − time 1 score); the independent variables were age, sex, National Adult Reading Test error score, the Motor Impairment Scale (MIS) score, duration of illness, and CAG repeat number. Analyses were carried out only for those tests that had demonstrated a statistically significant change at least at the $p < .005$ level: category and letter fluency, Stroop, object recall, and picture sequencing errors. Data were screened for outliers, which were removed from the analysis. No more than one outlier was detected for any dependent variable, and comparison with the results of analysis when outliers were included indicated minimal difference to the overall pattern of results.

The analyses yielded regression coefficients for each independent variable, with *t* tests for those coefficients. The analyses indicated that MIS scores contributed significantly to the variance of change scores in the case of the Stroop word 1 read ($t = 3.6$, $p = .001$) and word 2 read conditions ($t = 3.8$, $p = .001$) and to a lesser extent object memory test immediate recall ($t = 2.5$, $p = .02$). Duration of illness contributed additionally only to change in object memory immediate recall ($t = 2.2$, $p = .04$). Premorbid ability, estimated by number of errors on the National Adult Reading Test, also made a small contribution in the case of the Stroop word 2 read condition ($t = 2.6$, $p = .02$) and object memory delayed recall ($t = 2.2$, $p = .03$). Age, sex, and CAG repeat length did not contribute to the variance. The degree of change on verbal fluency tasks was not influenced by any of the variables, nor was change in picture sequencing errors.

Correlational analyses revealed that duration and MIS scores were significantly intercorrelated, suggesting that both may be regarded as markers of the course of disease. However, MIS scores were the better predictor of the magnitude of cognitive change as indicated by the regression analyses and by simple correlations. They correlated with change in Stroop word 1 read ($r_s = 0.56$, $p = .001$) and word 2 read times ($r_s = 0.48$, $p = .002$) and also with change in immediate object recall scores ($r_s = 0.45$, $p < .001$). Duration of illness correlated only with change in Stroop CB name times ($r_s = 0.39$, $p = .011$) and immediate object recall scores ($r_s = 0.40$, $p < .001$).

To determine the precise nature of the effect on cognitive change of disease severity, the patient sample was divided into two subgroups: those with an MIS score below the group median (MIS< 6.5) and those with scores above the median (MIS > 6.5). The data were reanalyzed for these separate subgroups. Significant change in memory performance on the object recall test was present only in patients with more severe illness (Table 5). Also change in error scores on picture sequencing was detected only in more advanced patients.

Cognitive Change Over 3 Years

The pattern of findings over 3 years in a smaller group of 31 patients was largely similar to that demonstrated in the larger group over 1 year (Table 6). There were significant differences in speed-based tasks (months of the year recitation, verbal fluency, and Stroop Test) and in immediate and delayed object recall. Conversely, performance on the Road Map Test of Directional Sense, measured by accuracy and completion time, and performance on the Wisconsin Card Sorting Test, measured by categories achieved, total errors, perseverations, and completion time showed no significant change.

Relationship Between Cognitive Performance and Motor Disability

Cross-sectional correlative analyses of patients at the time of their initial assessment revealed significant relationships between cognitive test performance and motor function (Table 7). Stronger and more consistent associations were present for non-choreic aspects of movement disorder than for chorea. In part, differences in significance level can be attributed to differences in statistical power arising from different group numbers. MIS data were available for all 82 patients, whereas chorea data (derived from the QNE) were available for only 52: measures of chorea in recently recruited subjects were not included since these were derived from the UHDRS scale, which yields a measure of chorea that is not precisely equivalent to that of the QNE. Nevertheless, inspection of correlation coefficients suggests that differences in group size is not the sole explanation of statistical differences. MIS scores are typically more strongly associated with cognitive measures than are chorea scores. The strongest associations with MIS scores typically occurred for cognitive test measures relating to performance speed rather than accuracy.

DISCUSSION

The study indicates that cognitive change can be demonstrated in HD patients over a period as short as 1 year. Nevertheless test measures were not equally sensitive to change.

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Table 5. Change in cognitive test performance over 1 year as a function of level of motor disability[a]

		Wilcoxon (z) matched pairs Patient subgroup			
		MIS < median		MIS > median	
Test	Task condition	z	p	z	p
Months	forward completion time	0.60	n.s.	2.44	.008**
	back completion time	1.02	n.s.	0.41	n.s.
	back-forward time	1.27	n.s.	(1.71)	
Digit span	forwards	1.62	n.s.	1.23	n.s.
	backwards	0.47	n.s.	1.74	n.s.
Road map	% correct	0.52	n.s.	0.71	n.s.
	completion time	0.40	n.s.	0.08	n.s.
	tracing time	1.96	.03*	0.13	n.s.
	completion-tracing time	1.05	n.s.	0.80	n.s.
Object recall	immediate	0.13	n.s.	3.09	.001**
	delayed	1.51	n.s.	1.95	.03*
Story recall	immediate	0.14	n.s.	1.60	n.s.
	delayed	0.22	n.s.	1.42	n.s.
Word fluency	animals/1 min	1.60	n.s.	3.10	.001**
	F words/1 min	3.30	.000***	2.34	.01*
Card sort	categories	1.70	n.s.	0.85	n.s.
	total errors	1.69	n.s.	1.50	n.s.
	% perseverations	0.97	n.s.	0.21	n.s.
	completion time	0.29	n.s.	0.32	n.s.
	dealing time	2.12	.02*	1.38	n.s.
	completion-dealing time	0.91	n.s.	1.16	n.s.
Picture sequencing	errors	1.08	n.s.	2.36	.009**
	completion time	0.47	n.s.	1.83	.03*
Stroop	word 1 read time	2.02	.02*	2.85	.002**
	word 2 read time	2.51	.006**	2.63	.005**
	CB name time	2.39	.008**	1.61	n.s.
	CW name time	1.06	n.s.	0.36	n.s.
	CW name errors	0.86	n.s.	1.48	n.s.
	CW-CB name time	1.17	n.s.	0.36	n.s.

[a]MIS: Motor Impairment Scale. Wilcoxon z scores are expressed as positive numerals for clarity. p values are shown in parenthesis if change in performance is not in the predicted direction of poorer performance on Test 2 than Test 1. n.s.: not significant. p values are shown to 3 decimal places; $p = .000$ implies that $p < .0005$.
***$p < .0005$; **$p < .01$; *$p < .05$.

Highly significant differences were found over 1 year in letter fluency (generating words beginning with F), in object recall, and on the Stroop Test. In contrast, the modified Wisconsin Card Sorting Test and accuracy scores on the Road Map Test of Directional Sense failed to reveal change even over a period of 3 years.

Differential sensitivity to change is likely to some extent to reflect characteristics of the tests themselves: the size of the response field (the range of possible scores) and gradation between scores. The Digit Span Test, for example, has a narrow response field, placing severe constraints on the test's capacity to detect small gradations of change. In the case of the Road Map Test responses for individual trials are not wholly independent, so that the test may be less sensitive to subtle gradations in performance than other tests. Moreover, although the Road Map Test differentiated HD patients from healthy controls, group differences were less marked than for other tests, perhaps because of wide normal variation in performance.

Timed measures putatively permit detection of subtle changes in performance. Nevertheless, not all timed measures showed change. The Wisconsin Card Sorting Test elicited no change even over 3 years, irrespective of whether performance was measured by categories, errors, or completion time. This is despite the test's established sensitivity to the presence of HD, and despite significant correlations between Card Sorting Test performance and neurological markers of disease demonstrated by cross-sectional analyses of the patient cohort. The lack of change is not due to floor effects, since a range of performance was demon-

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Table 6. Change in cognitive test performance over 3 years[a]

	Task condition	Test 1		Test 4		Wilcoxon	
Test	Median Range	Median	Range	Median	Range	*z*	*p*
Months	forward completion time	8	5–20	10	5–37	2.9	.002**
	back completion time	21	8–>	37	10–>	2.7	.004**
	back-forward time	14	2–>	18	5–>	0.8	n.s.
Digit span	forward	5	3–9	5	3–8	2.0	.02*
	backward	4	1–7	3	1–5	3.3	.000***
Road Map	% correct #	84	44–100	84	37–97	0.3	n.s.
	completion time	175	62–>	176	55–>	1.3	n.s.
	tracing time	37	18–75	46	18–>	2.2	.02*
	completion-tracing time	99	41–>	108	25–>	0.3	n.s.
Object recall	immediate (max 20)	7	3–12	5	1–11	2.4	.007**
	delayed (max 20)	5	0–12	4	0–10	2.9	.002**
Story recall	immediate (max 14)	5	0–12	4	0–13	0.0	n.s.
	delayed (max 14)	4	0–12	3	0–12	0.0	n.s.
Word fluency	animals/1 min	12	5–24	10	2–23	3.1	.001**
	F words/1 min	7	0–19	4	0–15	3.0	.002**
Wisconsin Card Sorting Test	categories (max 8)	4	0–7	3	0–7	1.5	n.s.
	total errors (max 48)	15	2–38	17	3–48	1.3	n.s.
	% perseverations	25	0–67	36	0–100	1.2	n.s.
	completion time	497	255–>	519	229–>	1.3	n.s.
	dealing time	70	62–125	90	47–188	1.2	n.s.
	completion-dealing time	410	234–>	364	166–>	0.2	n.s.
Picture sequencing	errors (max 24)	2	0–16	4	0–22	1.2	n.s.
	completion time	247	95–>	257	91–>	1.3	n.s.
Stroop	word 1 read time	63	50–110	94	50–330	1.9	.03*
	word 2 read time	64	48–115	99	50–700	2.4	.008**
	CB name time	105	76–183	163	90–620	2.9	.002**
	CW name time	175	105–320	415	140–873	2.9	.002**
	CW name errors	3	0–36	4	0–45	0.1	n.s.
	CW-CB name time	56	20–174	228	44–570	2.7	.004**

[a]max: maximum score possible; # chance level performance = 50% correct. For completion times ">" implies that time exceeds cut-off for task, usually indicating failure to complete the task. Wilcoxon *z* scores are expressed as positive numerals for clarity. n.s.: not significant ($p > .05$). *p* values are shown to 3 decimal places; $p = .000$ implies that $p < .0005$.
***$p < .0005$; **$p < .01$; *$p < .05$.

strated at baseline. Moreover, it was independent of stage of disease. Severely affected patients with high MIS scores showed no change as well as did mildly affected patients with low MIS scores. One possible interpretation is that the test is susceptible to practice effects. Such an interpretation is speculative. Nevertheless, if correct it would have significant practical implications. The test, widely used in the assessment of HD both in its original (Berg, 1948) and modified version (Nelson, 1976) and whose value in cross-sectional studies is unquestioned, may nevertheless have limited use in the longitudinal evaluation of patients. The possibility that HD patients might benefit from practice, moreover, introduces a note of caution to the interpretation of longitudinal data. In the present study, 3-year follow up data were derived from patients who had already participated in testing three times. Whether such familiarity with test procedures influences the observed rate of change remains uncertain. A study which compares the degree of change over 3 years in patients retested annually with those reexamined only once at the end of 3 years would address directly the contribution of practice.

The test results reveal more than properties of psychological test instruments. The findings corroborate those of others in pointing to the importance of psychomotor speed in characterizing the deficits in HD. The pattern of change over 1 year in Stroop Test scores reveals, however, an intriguing feature. Although changes were apparent for each of the four test conditions, the greatest changes occurred not as might be anticipated for the most cognitively demanding interference condition of naming word colors but for the least demanding conditions of word reading. The apparently systematic inverse relationship between magnitude of change and cognitive demands across the four test conditions suggests that this is not a chance effect. Indeed, sim-

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Table 7. Relationship at baseline testing between cognitive test scores and neurological disorder[a]

		QNE Chorea scale		MIS scale	
Test	Task condition	r_s	p	r_s	p
Months	forward completion time	0.19	n.s.	0.31	.007**
	back completion time	0.12	n.s.	0.49	.000***
	back-forward time	—		0.36	.003**
Digit span	forwards	0.25	n.s.	0.19	n.s.
	backwards	0.17	n.s.	0.38	.001**
Road map	% correct	0.00	n.s.	0.30	.009**
	completion time	0.09	n.s.	0.47	.000***
	tracing time	0.41	.008**	0.59	.000***
	completion-tracing time	—		0.31	.02*
Object recall	immediate (max 20)	0.31	.02*	0.23	.04*
	delayed (max 20)	0.35	.01*	0.40	.001**
Story recall	immediate (max 14)	0.12	n.s.	0.17	n.s.
	delayed (max 14)	0.18	n.s.	0.17	n.s.
Word fluency	animals/1 min	0.40	.004**	0.49	.000***
	F words/1 minute	0.29	.05*	0.51	.000***
Card sort	categories (max 8)	0.13	n.s.	0.44	.000***
	total errors (max 48)	0.19	n.s.	0.29	.01*
	% perseverations	0.16	n.s.	0.18	n.s.
	completion time	0.37	.01*	0.34	.005**
	dealing time	0.46	.02*	0.65	.000***
	completion-dealing time	—		0.32	.03*
Picture sequencing	errors (max 24)	0.05	n.s.	0.40	.000***
	completion time	0.27	n.s.	0.34	.004**
Stroop	word 1 read time	0.27	n.s.	0.46	.001**
	word 2 read time	0.25	n.s.	0.47	.001**
	CB name time	0.18	n.s.	0.49	.000***
	CW name time	0.26	n.s.	0.46	.001**
	CW name errors	0.11	n.s.	0.37	.008**
	CW-CB name time				

[a]QNE: Quantitated Neurological Examination. MIS: Motor Impairment Scale. For the Chorea Scale $n = 52$, MIS scale correlations based on complete group. n.s.: not significant. p values are shown to 3 decimal places; $p = .000$ implies that $p < .0005$.
***$p < .0005$; **$p < .01$; *$p < .05$.

ilar findings have been recorded by others (Bamford et al., 1995). Moreover, a comparable trend was observed in other tasks. The time to recite the months of the year in reverse order did not change over 1 year, but in a forward direction the change reached significance. The time to make left–right judgments on the Road Map Test did not change, but to trace the map did so. The time to complete the Card Sorting Test did not change, but the time to deal cards did so. In view of the large number of correlations, there is a need for caution in placing weight on individual results where statistical effects are small. Nevertheless, the fact that findings were invariably in the same direction, the less cognitively demanding of a pair of tasks showing the significant change, suggests a trend that should not be discounted.

The observed differential effect for less demanding tasks cannot be accounted for in simple motor terms. The four conditions of the Stroop Test and the respective components of the months of the year, Road Map and Wisconsin Card Sorting Test are largely equated for motor demands, so that alterations in motor skills *per se* should have a comparable effect across each component of the task. How then is it possible to interpret these apparently counterintuitive findings?

An intuitively plausible explanation is that performance on cognitively demanding tasks is compromised very early in the course of HD and is already substantially impaired at the time of patients' assessment (typically in stage II illness), whereas performance on easier tasks is only beginning to show change, hence the detection of change for easy but not difficult tasks. Against this notion is the finding that highly significant differences between HD and control performance already exist at baseline assessment for easy as well as difficult tasks. Moreover, HD subjects are not dis-

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proportionately slower than controls at baseline assessment in carrying out difficult compared to easy tasks.

An alternative possible explanation is that it is the "automatic" nature of the cognitive task that is the determining factor underlying the differential degree of change detected over 1 year. Reading words or naming block colors in the Stroop Test is, under normal circumstances, readily automatized since the range of responses is constrained and the same words are repeated multiple times. Similarly, reciting the months of the year is overlearnt and relatively automatic. It is the potential for execution as a relatively automatic program of responses, or behavioral routine, that accounts for the rapid response times in normal subjects. If HD patients are impaired in their ability to implement and execute an automatic response program, then this would have a disproportionate effect on undemanding tasks compared to cognitively demanding tasks that are under effortful rather than automatic control.

In view of the absence in this study of direct correlates with structural and functional brain imaging, inferences about underlying anatomy must necessarily be regarded as speculative. Nevertheless, it is well established that the basal ganglia have a critical role in the execution of motor programs (Marsden, 1982; Marsden & Obeso, 1994). It would be reasonable to infer that the impairments in "automatic" functioning observed in HD patients relate to disturbances in basal ganglia function. It is relevant in this regard that changes in basal ganglia volume in HD patients have been demonstrated by magnetic resonance imaging over relatively short time periods of 1–3 years (Aylward et al., 1997). Moreover, functional imaging studies (Beckman et al., 1997; Lawrence et al., 1996; 1998) using dopamine positron emission tomography (PET) markers have shown a link between cognitive impairments and striatal dysfunction. An inference from the present data is that in HD mental tasks that are normally mediated by basal ganglia function are increasingly under effortful, cortical control.

The differential impairment for undemanding tasks is less evident in the 3-year follow-up data. The fact that these follow-up data were obtained from a substantially smaller group of patients raises the possibility of lack of statistical power in eliciting the effect. Alternatively, the proposed loss of automaticity of function may be only one component of a complex set of deficits that contribute to psychomotor slowing in HD. One possibility is that it represents an early feature of the disease process which gives way to more generalized slowing. Whether this is indeed the case remains to be determined. Evaluation of presymptomatic carriers of the HD gene and very early symptomatic patients would help to resolve the issue.

In the present study, cross-sectional analysis revealed highly significant relationships between cognitive impairment and neurological disorder, adding support to the notion of a common anatomical substrate. Correlations were particularly strong with respect to the MIS scale measure, which encompasses non-choreic aspects of the movement disorder such as motor speed.

The attribution of cognitive changes in HD to impaired basal ganglia function is not new (Dubois et al., 1995; Jacobs & Huber, 1992; Saint-Cyr et al., 1995). Indeed, it is implicit in the concept of subcortical dementia, a term initially applied to progressive supranuclear palsy (Albert et al., 1974) but very early adopted in relationship to HD (McHugh & Folstein, 1975). Moreover, recent correlative studies have highlighted the relationship between cognitive test performance and measures of caudate atrophy (Brandt et al., 1995) and functional measures of striatal function (Beckman et al., 1997; Lawrence et al., 1996, 1998).

Despite the increase in interest in HD in recent years, relatively few studies have been published that report changes in symptomatology over time. Of the few longitudinal studies most have been concerned with identifying factors that affect rate of change such as age of onset and CAG repeat length (Beckman et al., 1997; Brandt et al., 1996; Illarioshkin et al., 1994). A study of particular relevance is a prospective investigation carried out by Bamford et al. (1995). As in the present study, cognitive tasks varied in the degree to which they elicited significant change. The most significant and consistent decline occurred on psychomotor tests. The prominent change in Stroop Test performance occurred particularly in the less demanding of the test conditions. However, not all the findings so closely parallel the present results. The present study found significant change in memory function over a short period whereas Bamford et al. did not. Change in the present study was, however, noted only in more severely affected patients suggesting that stage of illness may be a relevant factor. Characteristics of the memory test itself may also be relevant. In the object recall task, the presentation of objects in a random array maximizes the need for self-generated structure and organization. If HD patients have increasing difficulty with organizational and strategic skills, then this would explain why change may be detected for this but not other memory tests and why it is present in later-stage patients. Although such an explanation is speculative, it would be consistent with the clinical observation that HD patients, while performing poorly on memory tests, do not exhibit a classical amnesia even in relatively advanced disease. The assumption would be that it is not memory *per se* which changes with time but executive skills, which have a secondary effect on the efficiency with which information is encoded and retrieved.

The study demonstrates that change can be detected on some cognitive tests over a period as short as 1 year, providing guidance for the types of tasks most appropriate for longitudinal studies of HD. It is worth emphasising, however, that these results derive from a relatively large group study. Despite significant group effects, numerical differences in performance for individual patients were actually very small. This reflects the fact that HD is a slowly progressive disease with development over many years. The implication is that detection of reliable change in individual patients or small groups of patients over such a short time period would be highly problematic. This clearly has implications for the design of small-scale therapeutic trials, whose

aim is to attenuate decline (as opposed to producing improvement) in cognition. Evaluation of patients would need to take place over a period substantially longer than 1 year to determine efficacy. The findings highlight limitations of standard cognitive instruments in detecting change in HD over short time periods.

In the past, a traditional assumption was that cognitive changes in HD inevitably reflected the spread of pathology to cerebral cortex. The present findings add to the growing body of evidence that emphasizes the important contribution of striatal dysfunction in giving rise to cognitive impairment. The study reinforces the importance of psychomotor speed in characterizing the deficits of HD. More particularly, it postulates a breakdown of automatic cognitive routines and suggests that in HD ostensibly automatic tasks necessitate more conscious control. The extent to which this feature is fundamental to the cognitive disorder of HD remains the subject for future study.

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